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10/069,454	02/26/2002	Levav Roiz	02/23357	8094

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

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DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,454	ROIZ ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,19 and 21-62* is/are pending in the application.

4a) Of the above claim(s) *8-14,21-44 and 53-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,15,16,19,45-52,61 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-26-04 has been entered.

Applicants' amendment filed 11-26-04 has been entered. Claims 1, 3, 5, 15 and 46-52 have been amended. Claims 1-16, 19 and 21-62 are pending and claims 1-7, 15, 16, 19, 45-52, 61 and 62 are under consideration.

Priority

1. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must **include the relationship** (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the **first sentence of the specification** following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

The amendment filed 11-26-04 regarding the priority of the present application still fails to point out the relationship between PCT/IL00/00514 and Application No. 09/385,411. Mere statement of "claims the benefit of the priority of" is insufficient. Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 2 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "substantially lacks ribonucleolytic activity" in claims 2 and 16 is vague and render the claim indefinite. It is unclear as to the metes and bounds of what would be considered "substantially lacks ribonucleolytic activity". The specification fails to specifically define the phrase "substantially lacks ribonucleolytic activity".

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7, 15, 16, 19, 45-52, 61 and 62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on the use of any ribonuclease of the T2 family proteins having an actin binding activity, which is either a recombinant protein or a non-recombinant protein. The specification only discloses that RNase B1 isolated from *Aspergillus niger* has actin binding activity.

The scope of the claims encompasses a genus of ribonucleases of T2 family proteins having actin binding activity, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The claims encompass known and unidentified ribonucleases of the T2 family proteins. The specification fails to provide the structural features of the ribonuclease of T2 family having actin binding activity. The specification only discloses that RNase B1 has actin binding activity. It is unclear what contributes to the actin binding in the ribonucleases of T2 family proteins. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure regarding actin binding by the ribonucleases of the T2 family proteins in the present application is insufficient to describe the genus.

Further, the claims read on the use of a recombinant RNase B1 protein. The specification fails to provide any information regarding the nucleotide sequence encoding the *Aspergillus niger* RNase B1 protein. Table 2 (specification, p. 19-20) of the specification fails to provide any prior art that discloses the nucleotide sequence encoding the *Aspergillus niger* RNase B1 protein. A search to the prior art also fails to obtain any information regarding the nucleotide sequence encoding the *Aspergillus niger* RNase B1 protein. It appears that no nucleotide sequence encoding the *Aspergillus niger* RNase B1 protein has been disclosed at the time of the invention.

Therefore, the limited information provided in the present invention is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed ribonucleases of the T2 family proteins having actin binding activity or a recombinant RNase B1 protein. Thus, it is concluded that the written description requirement is not satisfied for the ribonucleases of the T2 family proteins having actin binding activity or a recombinant RNase B1 protein as claimed.

6. Claims 1-7, 15, 16, 19, 45-52, 61 and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventively reducing the number of aberrant crypt foci (ACF) in a rat having **DMH-induced** colon cancer when non-recombinant RNase B1 is administered directly to the colon via osmotic micro-pump, or reducing the number of colon tumor, the tumor size, the number of ACFs or the tumor angiogenesis in a rat having **DMH-induced** colon cancer with oral administration of the non-recombinant RNase B1 microcapsules, and reducing the number and size of tumor, inhibiting the growth of tumor and

reducing angiogenesis of tumor in rats treated with osmotic pumps that directly deliver the non-recombinant RNase B1 to the colon, does not reasonably provide enablement for a method of preventing proliferation, development, tumor growth, tumorigenesis, colonization, differentiation or angiogenesis of abnormally proliferating cells, such as various tumor cells, in a mammalian subject by using any ribonuclease of the T2 family having an actin binding activity or its mutants that substantially lack ribonuclease activity, a method of treating, inhibiting, or reversing proliferation, development, tumor growth, tumorigenesis, colonization, differentiation or angiogenesis of abnormally proliferating cells, such as tumor cells, in a mammalian subject by using any ribonuclease of the T2 family having an actin binding activity or its mutants that substantially lack ribonuclease activity other than non-recombinant RNase B1 via various administration routes, or a method of treating, inhibiting, or reversing proliferation, development, tumor growth, tumorigenesis, colonization, differentiation or angiogenesis of any brain tumor, various tumors other than melanoma and colon cancer as disclosed, and any disease or disorder other than tumor, such as Hodgkin's disease, arthritis, rheumatoid arthritis, diabetic retinopathy, angiogenesis, restenosis, in-stent restenosis and vascular graft restenosis, in a mammalian subject by using RNase B1 having an actin binding activity or its mutants that substantially lack ribonuclease activity via various administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-7, 15, 16, 19, 45-52, 61 and 62 are directed to a method of preventing, treating, inhibiting, or reversing a process associated with abnormally proliferating cells including proliferation, development, differentiation, transformation, tumorigenesis, tumor growth,

colonization and angiogenesis in a mammalian subject, or reducing the size or number of tumors in a mammalian subject by using any ribonuclease of the T2 family having actin binding activity, such as RNase T2, RNase Rh, RNase M, RNase Trv etc, and a pharmaceutical composition containing a recombinant ribonuclease of the T2 family having actin binding activity. Claims 2 and 16 specify the ribonuclease of T2 family substantially lacks ribonucleolytic activity. Claim 4 specifies the type of proliferating cells are associated with the cited proliferative disorders or diseases. Claim 5 specifies the administration route, including oral administration, topical administration, transmucosal administration, and parenteral administration etc. Claims 6 and 19 specify the ribonuclease is RNase B1.

The specification discloses that RNase B1 preventively administered via osmotic micro-pump reduces the number of aberrant crypt foci (ACF) in a rat having **DMH-induced** colon cancer, and RNase B1 preventively administered via oral administration of microcapsules reduces the number of colon tumor, the tumor size, the number of ACFs or the tumor angiogenesis in a rat having **DMH-induced** colon cancer, and the number and size of tumor are reduced, the growth of tumor is inhibited and angiogenesis of tumor is reduced in rats treated with osmotic pumps that directly deliver the RNase B1 to the colon (e.g. specification, example 4). The claims encompass preventing, treating, inhibiting, or reversing proliferation, colonization, differentiation or development of abnormally proliferating cells, such as tumor cells, in a subject by using any ribonuclease of the T2 family having actin binding activity or its mutants that substantially lack ribonucleolytic activity via various administration routes.

A pharmaceutical composition implies "therapeutic effects" of said pharmaceutical composition for a particular disease or disorder *in vivo*. The specification fails to provide

adequate guidance and evidence that any member of T2 ribonuclease family having actin binding activity or its mutants that substantially lack ribonucleolytic activity or a pharmaceutical composition comprising said ribonuclease can prevent proliferation, colonization, differentiation or development of abnormally proliferating cells, or can treat any abnormally proliferating cells, such as tumor cells, or reduce tumor number and size and tumor angiogenesis with said ribonuclease other than RNase B1 so as to provide therapeutic effect in a subject via various administration routes.

The rat colon cancer model used for the preventive study of RNase B1 is induced by injections of Dimethylhydrazine (DMH). It was well known in the art that there are many different causes of tumor formation in vivo, for example, genetically speaking, a gene mutation or a combination of different gene mutations, or environmental element, such as UV radiation, X-ray radiation, asbestos, cigarette smoking, and various carcinogens, or a combination of genetic mutation(s) and environmental element(s). The mechanisms of tumor formation from those different causes set forth above could differ from each other dramatically in which numerous factors get in play to form various cancer types and these mechanisms of tumor formation are very likely different from the mechanism of colon cancer formation via injection of DMH of the present invention. The specification fails to provide adequate guidance and evidence for how to prevent a process associated with abnormally proliferating cells including proliferation, development, differentiation, transformation, tumorigenesis, tumor growth, colonization and angiogenesis in a mammalian subject by using any ribonuclease of the T2 family having actin binding activity. The specification fails to provide adequate guidance and evidence for how to prevent numerous different tumor formations that naturally occur in a

mammalian subject by using any ribonuclease of the T2 family having actin binding activity. The data regarding the preventive effect of RNase B1 on the DMH-induced colon cancer formation can not be extrapolated to prevention of various naturally occurring tumors or proliferation, development, differentiation, transformation, colonization and angiogenesis of abnormally proliferating cells in a mammalian subject by using any ribonuclease of the T2 family having actin binding activity. The specification fails to provide sufficient enabling disclosure for preventing a process associated with abnormally proliferating cells including proliferation, development, differentiation, transformation, tumorigenesis, tumor growth, colonization and angiogenesis in a mammalian subject by using any ribonuclease of the T2 family having actin binding activity.

The specification also fails to provide adequate guidance and evidence for how to treat, inhibit, or reverse proliferation, development, tumor growth, tumorigenesis, colonization, differentiation or angiogenesis of abnormally proliferating cells, such as tumor cells, in a mammalian subject by using any ribonuclease of the T2 family having an actin binding activity or its mutants that substantially lack ribonuclease activity other than non-recombinant RNase B1 via various administration routes so as to provide therapeutic effect in vivo.

Deshpande et al., 2002 (Critical Reviews in Microbiology, Vol. 28, No. 2, p. 79-122) reports that RNases from T2 family are widespread in distribution and encompass ribonucleases isolated from viruses, bacteria, protozoa, fungi, plants, and animals. Although they share some similar structural features it does not necessarily mean that they would have same biological functions with respect to preventing, treating, inhibiting, or reversing proliferation, development, tumor growth, tumorigenesis, colonization, differentiation or angiogenesis of abnormally

proliferating cells in vivo. There are about 50 known T2 family of ribonucleases having molecular weights ranging from 19kDa to 97kDa and they have diverse role in living organisms. They have dramatically different amino acid sequences. Very few information is available on the structure-function correlation except that of RNase Rh and RNase LE. As discussed above under 35 U.S.C. 112 first paragraph written description rejection, the specification fails to provide the structural features of the ribonuclease of T2 family having actin binding activity. The specification only discloses that RNase B1 has actin binding activity. It is unclear what contributes to the actin binding in the ribonucleases of T2 family proteins and whether any other ribonuclease of the T2 family proteins has actin binding activity. Different member of the T2 ribonuclease family would have distinct protein sequences and different biological functions. There is no evidence of record that member of the ribonuclease of T2 family other than RNase B1 would also bind to actin such that said ribonuclease could inhibit the germination or pollen tube growth, or reduce the clonogenicity of the cancer cells *in vitro* and *in vivo*. One skilled in the art at the time of the invention would not know how to use the ribonuclease of T2 family proteins other than RNase B1 to treat, inhibit, or reverse proliferation, development, tumor growth, tumorigenesis, colonization, differentiation or angiogenesis of abnormally proliferating cells, such as tumor cells, in a mammalian subject without knowing whether said ribonuclease has actin binding activity or not.

In addition, the claims read on the use of a recombinant RNase B1 protein. The specification fails to provide any information regarding the nucleotide sequence encoding the *Aspergillus niger* RNase B1 protein. A search to the prior art also fails to obtain any information regarding the nucleotide sequence encoding the *Aspergillus niger* RNase B1 protein. Therefore,

the specification fails to enable the use of a recombinant RNase B1 for the claimed pharmaceutical composition and methods.

Further, the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). In view of the diversity of tumor formation, unpredictability of the biological function of a protein from mere amino acid sequence, the lack of nucleotide sequence encoding RNase B1, and the lack of information

regarding the structural feature that contributes to the claimed RNase having actin binding activity, one skilled in the art at the time of the invention would not know how to prevent a process associated with abnormally proliferating cells including proliferation, development, differentiation, transformation, tumorigenesis, tumor growth, colonization and angiogenesis in a mammalian subject by using any ribonuclease of the T2 family having actin binding activity, or how to inhibit or reverse said process, or to treat any abnormally proliferating cells, such as tumor cells, or to reduce tumor number and size and tumor angiogenesis by using the claimed ribonuclease of T2 family having actin binding activity or its mutants that substantially lack ribonucleolytic activity other than RNase B1 or a pharmaceutical composition comprising said ribonuclease so as to provide therapeutic effect in a subject via various administration routes.

Applicant states that "[H]owever, actin binding activity of a ribonuclease is, in itself, cannot confer such therapeutic character, as is clearly demonstrated by the tumor promoting activity of angiogenin (ANG), an actin-binding RNase A (Hu et al., PNAS, 1991...and Kao et al., PNAS, 2002...) (see amendment, p. 17). Indeed, Kao et al., 2002 (PNAS, Vol. 99, No. 15, p. 10066-10071), report that angiogenin is a potentially important target for anti-cancer therapy and inhibitor of ANG, 65828, significantly delayed the formation of subcutaneous tumors from two distinct human cancer cell types in athymic mice (e.g. abstract). Hu et al., 1991 (PNAS, Vol. 88, p. 2227-2231) state that angiogenin is a potent blood vessel inducer and its ribonucleolytic activity is essential for neovascularization (e.g. p. 2227, left column). It appears that a ribonuclease having actin binding activity can promote tumor formation rather than inhibit tumor growth or formation in vivo. This adds to the unpredictability of whether a ribonuclease of T2 family having actin binding activity can inhibit or reverse a process associated with abnormally

proliferating cells including proliferation, development, differentiation, transformation, tumorigenesis, tumor growth, colonization and angiogenesis in a mammalian subject.

The specification also fails to provide adequate guidance and evidence for how to treat, inhibit, or reverse proliferation, development, tumor growth, tumorigenesis, colonization, differentiation or angiogenesis of any brain tumor, leukemia, various tumors other than melanoma and colon cancer as disclosed, and any disease or disorder other than tumor, such as Hodgkin's disease, arthritis, rheumatoid arthritis, diabetic retinopathy, angiogenesis, restenosis, in-stent restenosis and vascular graft restenosis, in a subject by using RNase B1 having an actin binding activity or its mutants that substantially lack ribonuclease activity via various administration routes so as to provide therapeutic effect in vivo.

It was well known in the art that brain is separated from general circulation by the blood brain barrier. Castro et al., 2001 (Histl. Histopathol., Vol. 16, p. 1225-1238) points out that the brain offers a particular challenge for gene delivery to its constituent cells because it is "made up of mostly non-dividing cells, the skull limits direct injection of vectors into the brain, the blood brain barrier inhibits the easy entry of vectors injected into the bloodstream, and post mitotic target cells restrict what type of vector can be used to deliver genes to the brain" (e.g. abstract). "The main challenges holding back the widespread clinical implementation of neurological gene therapy are technical limitations of current transgene delivery system, i.e. the gene transfer vectors...short term expression of the potentially therapeutic transgenes, coupled to the instability of vectors in the presence of the inflammatory and immune responses directed against the vectors and/or transgenes, reduce the efficiency of delivered therapeutic transgenes...Factors affecting vector stability in target cells/tissues, remain to be identified" (e.g. page 1226, right column).

Similarly, there is the brain-barrier to the delivery of a protein, such as RNase B1 protein, to the brain.

The specification states that "In rats fed with encapsulated RNase B1, the effect of the treatment was less significant than that obtained by osmotic pumps...a very small proportion of the protein reaches to the colon. As mentioned before, the microcapsules indeed pass the stomach, but they still have a long route through the small intestine and the cecum". The specification further indicates that "orally administered RNase B1 did not decrease the number and size of pre-existing tumors" (e.g. p. 51-52). Therefore, administration route of the protein plays an important role in the efficiency of delivering the protein to target cells and providing therapeutic effects in vivo but the specification fails to provide sufficient enabling disclosure for the full scope of the invention claimed.

Further, there are various barriers before a protein can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids, and as discussed above, there is blood-brain barrier for treating brain tumors. The claims encompass numerous different diseases or disorders including papilloma, kaposi's sarcoma, melanoma, lung cancer, ovarian cancer, prostate cancer, astrocytoma, head cancer, neck cancer, bladder cancer, breast cancer, thyroid cancer, leukemia, Hodgkin's disease, Burkitt's disease, arthritis, rheumatoid arthritis, diabetic retinopathy, restinosis, vascular graft restenosis etc. The claims encompass treating abnormally proliferating cells residing at various locations all over the body of a mammalian subject. Thus, the effectiveness of the T2 family RNases or their mutants on preventing, inhibiting, or reversing the abnormally proliferating cells associated with various

diseases or disorders would depend on administration route of the claimed RNases and may also depend on their concentrations. Administration routes of the claimed RNases will determine whether sufficient RNases can reach target cells so as to provide therapeutic effect for preventing, inhibiting, or reversing various abnormally proliferative cells associated with different disorders or diseases in vivo. Further, each member of T2 family RNases has different biological function and the effective amount of RNase at the target cells could vary, therefore, one skilled in the art at the time of the invention would require undue experimentation to determine the amount of the RNase administered and the administration route for said RNase so as to provide therapeutic effect for various diseases and disorders in vivo for the full scope of the invention claimed.

The specification of the present application and the attached child application No. 10/952,495 in the amendment filed 11-26-04 only disclose inhibition of tumor growth or reduction of tumor size of colon cancer and melanoma with RNase B1 via different administration routes, including oral administration, minipump administration, intraperiponeal administration and intravenous administration. However, the specification of the present application and application No. 10/952,495 fail to provide adequate guidance and evidence for how to treat, inhibit, or reverse proliferation, development, tumor growth, tumorigenesis, colonization, differentiation or angiogenesis of any brain tumor, leukemia, various tumors other than melanoma and colon cancer as disclosed, and any disease or disorder other than tumor.

As discussed above, it was well known in the art that there are many different causes of tumor formation in vivo, for example, genetically speaking, a gene mutation or a combination of different gene mutations, or environmental element, such as UV radiation, X-ray radiation,

asbestos, cigarette smoking, and various carcinogens, or a combination of genetic mutation(s) and environmental element(s). The mechanisms of tumor formation from those different causes set forth above could differ from each other dramatically in which numerous factors get in play to form various cancer types and these mechanisms of tumor formation are very likely different from the mechanism of colon cancer formation via injection of DMH of the present invention. Likewise, the mechanisms of formation of those non-tumor disease or disorders, such as Hodgkin's disease, arthritis, rheumatoid arthritis, diabetic retinopathy, restinosis, vascular graft restenosis etc., also differ from that of colon cancer formation or melanoma formation. The data regarding treatment of colon cancer and melanoma with RNase B1 can not be extrapolated into success for treating other tumors and other non-tumor diseases or disorders. There are various barriers before a protein can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids, protein stability, and blood-brain barrier for treating brain tumors. The effectiveness of the RNases B1 or their mutants on preventing, inhibiting, or reversing the abnormally proliferating cells associated with various diseases or disorders would depend on administration route of the RNases B1, the location of the disease or disorder within the mammalian subject, and the type of disease or disorder targeted.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicant amends the claims to read on using ribonuclease of T2 family protein having actin binding activity and cites US Patent Application No. 10/952,495. Applicant argues that i.p. administration of T2 ribonuclease shows inhibition of subcutaneous tumors of melanoma and colon cancer cells, reduction of the number of lung melanoma metastases, and intravenous administration of the T2 ribonuclease shows inhibition of colon tumor growth and number of lung melanoma metastases in vivo, and i.p. administration of RNase B1 inhibits angiogenin-dependent neovascularization of sponge implants (amendment, p. 14-21). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph rejection and that the data presented in the present application and U.S. Patent Application No. 10/952,495 is limited to the use of RNase B1 isolated from *Aspergillus niger*.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are

available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER